REMARKS/ARGUMENTS

Claims 3-16 are pending in the application. Claims 6-11 are withdrawn from consideration. Claims 3-5 and 12-16 stand rejected. Applicant now addresses the Examiner's comments and claim rejections in the order presented in the office action to the extent that they might be applied to pending Claims 3-5 and 12-16.

Rejection under Judicially Created Doctrine of Obviousness-type Double Patenting

Claims 3-5 and 12-16 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 8-15 of U.S. Patent No. 6,384,076. The Office Action indicates that a timely filed terminal disclaimer in compliance with 37 C.F.R. §1.321(c) may be used to overcome this rejection.

A Terminal Disclaimer to Obviate a Double Patenting Rejection over a Prior Patent and a Statement under 37 C.F.R. §3.73(b) signed by the assignee are being filed concurrently herewith. Accordingly, Applicant requests that this rejection of Claims 3-5 and 12-16 be withdrawn.

Rejection under 35 U.S.C. §102

Claims 3-5 and 12-16 stand rejected under 35 U.S.C. §102(b) as anticipated by Edmundson et al. (WO 98/13062). The Examiner contends that (1) Edmundson et al. discloses a method for treating various forms of arthritis such as rheumatoid arthritis by administering APM and alkyl derivatives; (2) Medline abstracts 90333175, 93088234 and 95072271 establish that patients with rheumatoid arthritis have higher or significantly higher blood viscosity, showing what would have been inherent in Edmundson et al's claims and disclosure; (3) Edmundson et al treated all rheumatoid arthritic patients and at least some of them must necessarily have had high whole blood viscosity or abnormally viscous whole blood; and (4) because the same patients were treated with APM and alkyl ester derivatives with the same dosage, the same therapeutic results (reduction in whole blood viscosity in a patient) must necessarily have been obtained, the claims in the present application are anticipated. Applicant traverses this rejection for reasons given below.

In WO 98/13062 at Page 18, line 23 through Page 23, line 34, Edmundson et al present data in transgenic mice (known to be a useful model for studying anti-TNF-α and other agents for treatment of RA) that indicate APM-treated mice experienced less loss of function, less joint swelling and apparently less vasculitis than the untreated controls. In no way does WO 98/13062 teach or suggest that APM is an effective treatment for high whole blood viscosity or abnormally viscous whole blood in an RA patient. Therefore, WO 98/13062 does not anticipate the present application.

For inherent anticipation, the claimed element necessarily must always be found in the composition or result in the process disclosed in the cited prior art reference. Inherency may not be based on possibilities. The Federal Circuit addressed anticipation issues in Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 20 USPQ 2d 1746 (Fed.Cir. 1991). In discussing the anticipation by inherency doctrine, the court stated:

> To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. . . . Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. . . . If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, seems to be well settled that the disclosure should be regarded as sufficient.

Continental Can, 948 F.2d at 1268-69.

In order for Edmundson et al to inherently anticipate the present application, it requires that *every* patient treated for rheumatoid arthritis (hereinafter "RA") according to the method of Edmundson et al would have the condition of high whole blood viscosity or abnormally viscous blood. Applicant submits that not all RA patients have high whole blood viscosity or abnormally viscous blood. Moreover, the references cited in the office action do not support the possibility that all RA patients have high whole blood viscosity or abnormally viscous blood.

Balabanova et at (Medline Accession No. 90333175) discloses a study of RA patients with systemic manifestations and high laboratory activity. In particular, the hyperviscosity of the blood in patients with systemic manifestations was linked to the presence of pathological

immune complexes in the blood. This study concentrated on one particular subgroup of RA patients (i.e., patients with systemic manifestations, e.g., rheumatoid nodules, rheumatoid vasculitis, and ocular, respiratory, cardiac, hematologic, and neurologic complications); it did not include other types of RA patients such as those experiencing oligoarticular illness of brief duration. From this study, a person skilled in the art would not conclude that *all* RA patients have high whole blood viscosity or abnormally viscous blood.

Sundukov et al (Medline Accession No. 93088234) also discloses a study of RA patients with systemic manifestations. As discussed above, since this study only included patients with systemic manifestations, a person skilled in the art would not conclude that *all* RA patients have high whole blood viscosity or abnormally viscous blood.

Gudmundsson et al (Medline Accession No. 95072271) discloses a study of different methods of measuring whole blood viscosity using a couette rotational viscometer for the purpose of developing a method of testing the blood samples of RA patients to best differentiate between the viscosities of RA patients and healthy controls. Gudmundsson et al discloses a specific method by which native or whole blood viscosity, corrected blood viscosity, plasma viscosity and red cell aggregation were all significantly higher in the RA patients tested than in controls. Gudmundsson et al does not specify the types of patients involved in this particular study; however, given that the purpose of this study was to maximize the differences between the whole blood viscosity levels of RA patients and controls, it would seem reasonable that Gudmundsson et al would have selected patients known to have high whole blood viscosity. In no way does Gudmundsson et al indicate that his study included patients representative of all types of RA patients or that his test results are representative of *all* RA patients.

Reported laboratory findings for RA indicate a consensus that while no tests are specific for diagnosing the disease, blood tests can be helpful (copies attached at **Tab A** and **Tab B**: *Harrison's Principles of Internal Medicine*, 14th ed., AS Fauci, E Braunwald, KJ Isselbacher, JD Wilson, JB Martin, DL Kasper, SL Hauser, and DL Longo, eds., McGraw-Hill, New York, New York; 1998, vol. II, p. 1884; and The Merck Manual, 16th ed., R Berkow and AJ Fletcher, eds., Merck & Co., Inc., Rahway, New Jersey; 1992, p. 1306). Exemplary blood tests include the

presence of normochromic-normocytic anemia and/or thrombocytosis, elevated erythrocyte sedimentation rate (ESR), elevated plasma viscosity, presence of rheumatoid factor, and elevated acute phase reactants such as ceruloplasmin and C-reactive protein. Elevated ESR was noted in 90% of active RA cases; however, increased sedimentation of red blood cells is not indicative of increased whole blood viscosity. Likewise, elevated plasma viscosity was considered equally sensitive to elevated ESR; however, plasma viscosity is not indicative of whole blood viscosity. High whole blood viscosity or abnormally viscous blood were not listed in these as being diagnostic of RA. Moreover, Bull et al reported a consensus analysis devised to assess the performance of 31 laboratory tests commonly used to monitor acute and chronic inflammatory diseases, and in 17 RA patients, plasma viscosity and ESR (reportedly found in 90% of RA patients with acute disease) were ranked in first place and the measurement of acute-phase serum protein orosomucoid ranked third as being the most useful tests (Bull, et al. 1986. "Ranking of laboratory tests by consensus analysis," *Lancet* 2:377-380; abstract at **Tab C**). High whole blood viscosity and abnormally viscous blood did not rank as one of the top three tests, providing further evidence that these conditions are not always found in RA patients.

In summary, there are enough conflicting reports about laboratory findings in RA patients to show that a person skilled in the art would not conclude that *all* RA patients have high whole blood viscosity or abnormally viscous blood or that it would represent proof of disease. Nor would a person skilled in the art conclude from the teachings of WO 98/13062 that treatment of RA with APM and/or its derivatives would result in lowering high whole blood viscosity or abnormally viscous blood. In Example 5 of WO 98/13062, Applicant presents data that show APM and/or derivatives lowering the deleterious effects of TNFα in transgenic mice accepted as an animal model for studying RA. It is also well known in the art that bone loss is associated with RA; and WO 98/13062 discloses APM and/or derivatives decreasing synovial swelling, bone thickening tenderness after 6 months treatment and decreasing bone readsorption after 15 months treatment in an RA patient (Page 16, lines 18-30). Thus, based on WO 98/13062, a person skilled in the art would recognize the benefits of treatment with APM and/or derivatives for RA to include reduction in TNFα effects and bone loss, and not use of APM and/or derivatives to reduce high whole blood viscosity or abnormally viscous blood.

For the foregoing reasons, Applicant believes that pending Claims 3-5 and 12-16 are not inherently anticipated by WO 98/13062 and respectfully requests that this rejection of these claims be withdrawn.

Applicant does not believe that any fee is required for this amendment. However, if this is error, please charge any necessary fee to Conley Rose's Deposit Account No. 50-1515.

Respectfully submitted,

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